nature publishing group

SPECIAL REVIEW

Reduced Dietary Salt for the Prevention of Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials (Cochrane Review)

Rod S. Taylor[1], Kate E. Ashton[2], Tiffany Moxham[3], Lee Hooper[4] and Shah Ebrahim[5]

BACKGROUND

Although meta-analyses of randomized controlled trials (RCTs) of salt reduction report a reduction in the level of blood pressure (BP), the effect of reduced dietary salt on cardiovascular disease (CVD) events remains unclear.

METHODS

We searched for RCTs with follow-up of at least 6 months that compared dietary salt reduction (restricted salt dietary intervention or advice to reduce salt intake) to control/no intervention in adults, and reported mortality or CVD morbidity data. Outcomes were pooled at end of trial or longest follow-up point.

RESULTS

Seven studies were identified, three in normotensives, two in hypertensives, one in a mixed population of normo- and hypertensives and one in heart failure. Salt reduction was associated with reductions in urinary salt excretion of between 27 and 39 mmol/24 h and reductions in systolic BP between 1 and 4 mm Hg. Relative risks (RRs) for all-cause mortality in normotensives (longest follow-up—RR: 0.90, 95% confidence interval (CI): 0.58–1.40, 79 deaths) and hypertensives (longest follow-up RR 0.96, 0.83–1.11, 565 deaths) showed no strong evidence of any effect of salt reduction CVD morbidity in people with normal BP (longest follow-up: RR 0.71, 0.42–1.20, 200 events) and raised BP at baseline (end of trial: RR 0.84, 0.57–1.23, 93 events) also showed no strong evidence of benefit. Salt restriction increased the risk of all-cause mortality in those with heart failure (end of trial RR 2.59, 1.04–6.44, 21 deaths).We found no information on participant's health-related quality of life.

CONCLUSIONS

Despite collating more event data than previous systematic reviews of RCTs (665 deaths in some 6,250 participants) there is still insufficient power to exclude clinically important effects of reduced dietary salt on mortality or CVD morbidity. Our estimates of benefits from dietary salt restriction are consistent with the predicted small effects on clinical events attributable to the small BP reduction achieved.

Keywords: *blood pressure; cardiovascular disease; diet; hypertension; meta-analysis; salt; sodium; systematic review*

This article is based on a Cochrane Review published in the *Cochrane Database of Systematic Reviews* (*CDSR*) YYYY, Issue X, DOI: 10.1002/14651858.CD00xxxx (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the *CDSR* should be consulted for the most recent version of the review.

A more detailed review has been published and will be updated in the Cochrane Database of Systematic Reviews [Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention Of cardiovascular disease. Cochrane Database of Systematic Reviews (CDSR) 2011, Issue X, DOI: 10.1002/14651858.CD00xxxx (see www.thecochranelibrary.com for information). This is a version of a Cochrane review, which is available in The Cochrane Library. Cochrane systematic reviews are regularly updated to include new research, and in response to feedback from readers. The results of a Cochrane review can be interpreted differently, depending on people's perspectives and circumstances. Please consider the conclusions presented carefully. They are the opinions of review authors, and are not necessarily shared by The Cochrane Collaboration.

American Journal of Hypertension, advance online publication 6 July 2011; doi:10.1038/ajh.2011.115

High dietary intake of salt has been identified as an important risk factor for cardiovascular disease (CVD). The current public health recommendations in most developed countries are to reduce salt intake by about half, i.e., from ~10 to 5 g/day.[1–4] However, the evidence for the reduction of CVD morbidity and mortality as the result of reduced salt intake remains controversial.[5]

A number of observational studies support the link between salt intake and CVD. A meta-analysis of 13 prospective studies including 177,000 participants reported a high salt intake was associated with a greater risk of stroke (RR, 1.23, 95% confidence interval (CI): 1.06–1.43).[6] However, there was no association between salt intake and all CVD events, and total mortality was not reported. Furthermore, the interpretation of this observational evidence base is complicated by the heterogeneity in estimating sodium intake (diet or urinary salt excretion), types of participants (healthy, hypertensive, obese, and nonobese), different end points, and definition of outcomes across studies.[5]

[1]Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK; [2]Clinical Trials and Evaluation Unit, University of Bristol, Bristol, UK; [3]Wimberly Library, Florida Atlantic University, Boca Raton, Florida, USA; [4]Norwich Medical School, University of East Anglia, Norwich, UK; [5]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK. Correspondence: Rod S. Taylor (rod.taylor@pms.ac.uk)

Received 1 May 2011; first decision 9 May 2011; accepted 9 May 2011.

The relationship of salt intake to blood pressure (BP) is the basis for the belief that restriction in dietary sodium intake will prevent BP-related CVD events.[7] A number of meta-analyses of randomized controlled trials (RCTs) of salt reduction and BP have been undertaken.[8,9] Although these analyses consistently report a reduction in the level of BP with reduced salt intake, the level of BP achieved is less impressive in the longer-term. A Cochrane review of RCTs of dietary salt restriction intervention of at least 6 months duration, found that intensive support and encouragement to reduce salt intake lowered BP at 13 to 60 months but only by a small amount (systolic by 1.1 mm Hg, 95% CI: 1.8–0.4, diastolic by 0.6 mm Hg, 95% CI: 1.5 to −0.3).[10] The reduction in BP appeared larger for people with higher BP. A decrease in BP is only important if it results in a decrease in CVD events and deaths. Sustained reductions in mean BP of 2–3 mm Hg are necessary for important population reductions in CVD events.[11] Whereas the Cochrane review also sought to assess the impact of dietary salt restriction on mortality and CVD events, across the included 11 RCTs there were only 17 deaths spread evenly across groups and 46 CVD events in the controls compared with 36 in low-sodium diet groups. This extremely low number of events substantially limited the ability of this review to detect small to moderate reductions in the risk of CVD events.

The aim of this study was to undertake an updated systematic review and a meta-analysis of RCT evidence to confirm whether a reduction in dietary salt is associated with improvements in mortality and CVD events.

METHODS

The study was carried out according to the methods recommended by the Cochrane Collaboration and written in accordance with the PRISMA statement for reporting systematic reviews.[12,13]

Search strategy. We searched several clinical databases up to October 2008: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, PsycINFO, Health Technology Assessment (HTA), Abstracts of Reviews of Effects (DARE), and the NHS Centre for Reviews and Dissemination (CRD) databases. Consideration was given to variations in terms used and spellings of terms so that studies were not missed and took the general form: ("*salt*" OR "*sodium*" OR (synonyms)') and ("*CVD*" or (synonyms)). Searches included a filter to limit to humans and controlled trials. No language or additional limits were included. An updated search of MEDLINE, EMBASE, and CENTRAL was undertaken (to March 2011). Reference lists of reviews and included articles were also examined for additional studies.

Inclusion criteria. Studies were selected for inclusion on the basis of the following criteria:

- Study design: RCTs (individual or cluster level allocation) with follow-up of at least 6 months.
- Types of participants: adults (18 years or older), irrespective of gender or ethnicity. Studies of children or pregnant women were excluded.
- Intervention: reduced dietary salt and could include studies that involved participants receiving a dietary intervention that restricted salt or studies where the intervention was advised to reduce salt intake.
- Comparator: control or placebo diet, or no intervention.
- Outcomes: Primary-mortality (overall and CVD), CVD morbidity (including fatal and nonfatal myocardial infarction, stroke, angina, heart failure, peripheral vascular events, sudden death, revascularization (coronary artery bypass surgery or angioplasty with or without stenting) and CVD-related hospital admissions. In studies that reported primary outcomes, we also sought the following secondary outcomes: systolic and diastolic BP, and urinary salt excretion (or other method of estimation of salt intake) and health-related quality of life using a validated outcome measure (e.g., Short Form 36 (ref. 14)).

Studies not reporting all-cause mortality or CVD events were excluded.

Selection of studies. The titles and abstracts of studies identified by the search strategy were independently screened by two reviewers (K.E.A. and R.S.T.) and clearly irrelevant studies discarded. In order to be selected, abstracts had to clearly identify the study design, an appropriate population and a relevant intervention/exposure, as described above. The full-text reports of all potentially relevant studies were obtained and assessed independently for eligibility, based on the defined inclusion criteria, by two reviewers (K.E.A. and R.S.T.). Any disagreement was resolved by discussion or where agreement could not be reached, by consultation with an independent third person (L.H.).

Data extraction and management. Standardized data extraction forms were used. Relevant data regarding inclusion criteria (study design, participants, intervention/exposure, and outcomes), risk of bias (see below) and outcome data were extracted. Data extraction was carried out by a single reviewer (K.E.A. or R.S.T.) and checked by a second reviewer (R.S.T. or K.E.A.). Disagreements were resolved by discussion or if necessary by a third reviewer (L.H.). We extracted outcomes at the last reported follow-up point within the trial, and also at the latest follow-up after the trial, where this was available; we reasoned this would maximize the number of events reported. Included study authors were contacted to clarify any missing outcome data or issues of risk of bias assessment.

Assessment of risk of bias in included studies. We assessed a number of risk of bias domains in studies meeting the inclusion criteria: random sequence generation and allocation concealment, description of dropouts and withdrawals, blinding (participants, personnel, and outcome assessment) and selective

outcome reporting.[12] In addition, evidence was sought that the groups were balanced at baseline, that intention-to-treat analysis was undertaken and whether the period over which the salt intervention lasted and follow-up of outcome were equivalent. The risk of bias of included studies was assessed by a single reviewer (K.E.A.) and checked by a second reviewer (R.S.T.). Disagreements were resolved by discussion or if necessary by a third reviewer (L.H.).

Data synthesis. For mortality and CVD events, a relative risk (RR) and 95% CI was calculated for each trial. For BP and urinary sodium excretion, mean group difference and 95% CI were calculated using weighted mean difference. Heterogeneity amongst included studies was explored qualitatively (by comparing the characteristics of included studies), and quantitatively (using the χ^2 test of heterogeneity and I^2 statistic).[15,16] Results from included studies were combined for each outcome to give an overall estimate of treatment effect at the latest point available within the randomized trial, and, as a secondary analysis, at the latest point available (including where participants were followed after the end of the randomization period). A fixed-effect meta-analysis was used except where statistical heterogeneity (χ^2 P value ≤0.05 and I^2 value ≥50%) was identified, in which case methodological and clinical reasons for heterogeneity were considered and a random-effects model was used.

We planned to explore various potential moderator effects (i.e., individual advice vs. population level interventions, level of baseline risk of CVD, salt reduction only interventions vs. multicomponent dietary interventions that include salt restriction, level of salt reduction achieved, baseline BP, and change in BP).[17] Additionally, we planned to use funnel plot and Egger *et al.*'s regression test for funnel plot asymmetry to examine the likely presence of publication bias and small-study effect.[18] However, an insufficient number of included studies prevented us from undertaking these analyses.

Analyses were done using the Review Manager (RevMan) software, Version 5.0 (The Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Study characteristics

Selection of studies is summarized in **Figure 1**. The characteristics of the seven included trials are summarized in **Table 1**. These trials were published in 39 papers.[19–57]

We included three trials in normotensives (HPT[20], TOHP I[33,34], TOHP II[34,45]; n = 3,518), two in hypertensives (Morgan *et al.*[30], TONE[51]; n = 758), and one in a mixed population of normo- and hypertensives (Chang *et al.*[19]; n = 1,981). The normotensive trials were in healthy individuals (predominantly white men, median age 40 years) with high-normal BP and all conducted in the USA. The three studies in hypertensive populations included one trial in treated hypertensives, two in participants with untreated hypertension (predominantly male, median age 66 years and mix of ethnicities) and were conducted in Australia, Taiwan, and USA. Sixty percent of participants in the Chang *et al.* study were defined as non-

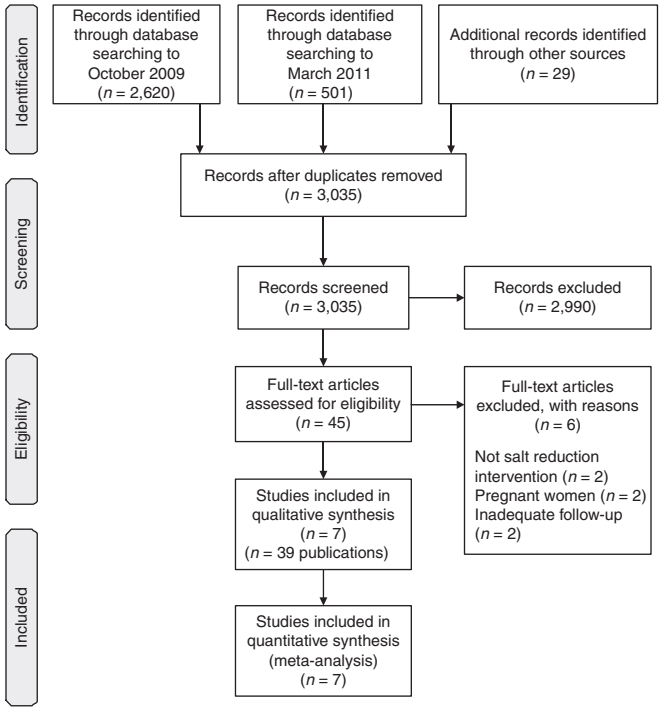

Figure 1 | Flow chart showing selection of studies.

hypertensive.[19] The final trial was undertaken in Italy and included participants diagnosed with heart failure (ethnicity not reported, mean age 73 years) who had been hospitalized for uncompensated heart failure within the previous 30 days and had a high-normal BP.[32]

Trials follow-up ranged across studies from 6 to 71 months postrandomization. A longer observational follow-up following the end of the randomized trial period was reported for the TOHP I (11.5 years)[34] and TOHP II (8 years)[34] trials and we were able to obtain longer observational unpublished data from the authors of the TONE study (12.7 years).

Six of the seven trials aimed to reduce salt intake by a range of approaches that included comprehensive dietary and behavior change programmes led by experienced personnel, including group counseling sessions, various types of advice and the provision of information leaflets. Intervention group sodium excretion goals were set at <70–100 mmol/24 h. Control groups received no active behavioral intervention or advice. In contrast, in the Chang *et al.* study,[19] participants received a dietary programme according to the cook of the kitchen to which they were assigned (cluster randomization) and were given either "high potassium salt" (low sodium) or "usual salt" (high sodium) diet. Intervention duration ranged across studies from 6 to 36 months. In the Paterna trial of patients with heart failure, in addition to either low-sodium or control diet, both groups received a high dose diuretic (furosemide, 250–500 mg b.i.d.).[32]

Risk of bias in included studies

A number of studies failed to give sufficient detail to assess their potential risk of bias. Details of generation and concealment of random allocation sequence were particularly poorly

Table 1 | Characteristics of included trials

Trial	Participants	Intervention	Control	Outcomes	Follow-up
Chang *et al.*[19] (Taiwan) Cluster	Normo- and hypertensive Mean age: 75 years, 100% male, 100% Asian Mean SBP: 131 and DBP: 71 mm Hg Not on AHTM	*N* = 768 (two kitchens) Ate prepared food using salt-containing 49% sodium chloride 49% potassium chloride and 2% other additives Target: not reported Duration: average 31 months	*N* = 1,213 (three kitchens) Ate food containing 99.6% sodium chloride and 0.4% other additives	Mortality (all cause and CVD)	31 Months postrandomization
HPT[20–29] (USA) Individual	Normotensive Mean age: 39 years, 65% male, 82% white Mean SBP: 124 and DBP: 83 mm Hg Not on AHTM	*N* = 196 Dietary counseling and behavioral change programme Target: USE ≤70 mmol Duration: 36 months	*N* = 196 No dietary counseling or behavior change	Mortality (all cause), BP, USE.	36 Months postrandomization
Morgan *et al.*[30,31] (Australia) Individual	Hypertensive Mean age: 57–59 years, 100% male, Mean SBP: 160–165 and DBP: 97 mm Hg On ATHM	*N* = 35 Instruction to reduce dietary sodium chloride intake Target: sodium intake 70–100 mmol/day Duration: 6 months	*N* = 42 No dietary instruction	Mortality (all-cause, CVD), CVD events, BP, USE.	Events: 7–71, BP: 24, USE: 6 months postrandomization
Paterna *et al.*[32] (Italy) Individual	Congestive heart failure Mean age: 73 years, 62% male Mean SBP: 125-126 and DBP: 82–83 On ATHM	*N* = 114 Received written standard diets Target: sodium intake 80 mmol/day Duration: 6.2 months	*N* = 120 Same diets advice but with addition of 40 mmol of sodium/day.	Mortality (all cause), BP, USE	6.4 Months postrandomization
TOHP I[33–44] (USA) Individual	Normotensive Mean age: 43 years, 71% male, 77% white, Mean SBP: 125 and DBP: 84 DBP mm Hg Not on AHTM	*N* = 327 Dietary and behavioral counseling Target: USE 80 mmol/day Duration: 18 months	*N* = 417 General guidelines for healthy eating	Mortality (all cause), CVD events, BP, USE	18 Months postrandomization Additional ~10 years observational follow-up for events
TOHP II[34,45–50] (USA) Individual	Normotensive Mean age: 44 years, 66% male, 66% white, Mean SBP: 127 and DBP: 86 mm Hg Not on AHTM	*N* = 1,191 Dietary and behavioral counseling Target: USE 80 mmol/day Duration: 36 months	*N* = 1,191 No advice	Mortality (all cause), CVD events, BP, USE	36 Months postrandomization Additional ~5 years observational follow-up for events
TONE[51–57] (USA) Individual	Hypertensive Mean age: 66 years, 53% male, 76% white, Mean SBP: 128 and DBP: 71 mm Hg On AHTM	*N* = 340 Individual and group dietary and behavioral counseling Target: USE < 80 mmol/day Duration: unclear	*N* = 341 Group meetings without dietary counseling	Mortality (all-cause, CVD), CVD events, BP, USE	30 months postrandomization Additional observational follow-up for events to 12.7 years postrandomization

ATHM, antihypertensive medication; BP, blood pressure; CVD, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure; USE, urinary sodium excretion.

reported (**Table 2**). However, in all cases there was objective evidence of balance in baseline characteristics of intervention and control participants. While studies reported loss to follow-up and reasons for this loss, few undertook analyses to assess the impact of these losses. In the TONE study, the authors state that data was collected via psychological questionnaires at randomization and a number of the follow-up visits. However, none of these data were found in the identified trial reports.[51–57] Although often not stated, all studies appeared to undertake an intention-to-treat analysis in that groups were analyzed according to initial random allocation. All studies assessed compliance to salt reduction intervention using diet diaries or monitoring urinary salt excretion. However, in the longer-term follow-up of the TOHP I, TOHP II, and TONE trials such compliance data were not reported. Therefore, it was unclear if intervention groups were encouraged to continue their low-salt diets or to return to their pretrial diet. Similarly, control groups may have been left to continue with their usual diet or advised to reduce their salt at the end of the trial.

Mortality and CVD events

Results are presented and pooled separately for normotensive, hypertensive, and heart failure studies. Outcomes were pooled at end of trial and at longest follow-up point.

All-cause mortality was reported at the end of the trial in six of the included studies (HPT[20]; TOHP I[33]; TOHP II[45]; Chang *et al.*[19]; Morgan *et al.*[30], and Paterna *et al.*[32]). Although there was weak evidence of a reduction in the number of deaths in the reduced salt group relative to controls for normotensives (fixed effects, RR 0.67, 95% CI: 0.40–1.12, 60 deaths in

Table 2 | Risk of bias of included trials

Trial name	Adequate sequence generation?	Adequate concealment?	Outcome blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Intention-to-treat analysis?	Groups balanced at baseline?	Assessment of dietary compliance?
Chang *et al.*[19]	Yes	Unclear	Unclear	No	Yes	Yes	Yes	Yes
HPT[20–29]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Morgan *et al.*[30]	Unclear	Unclear	Unclear	No	Yes	Yes	Yes	Yes
Paterna *et al.*[32]	Yes	Unclear	Unclear	No	Yes	Yes	Yes	Yes
TOHP I[33–44]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
TOHP II[34,45–50]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
TONE[51–57]	Yes	Yes	Yes	No	Unclear	Yes	Yes	Yes

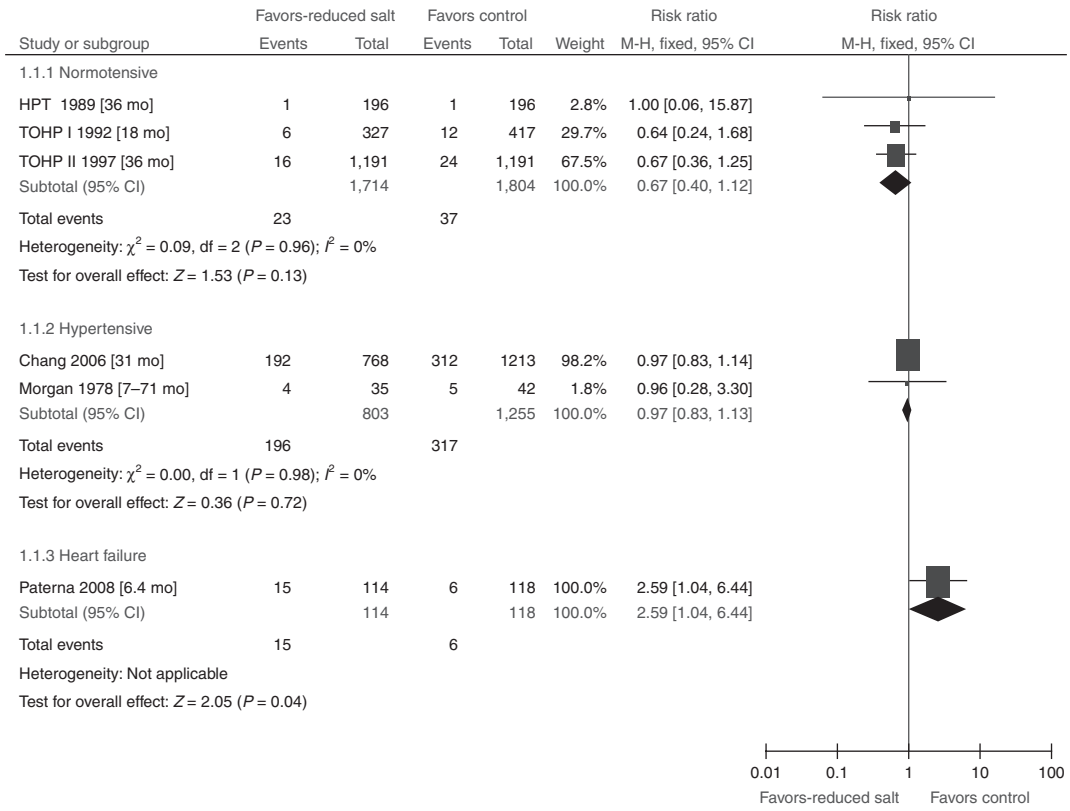

Figure 2 | All-cause mortality at end of trial. Duration of follow-up reported in parentheses.

total, χ^2 *P* value = 0.96, I^2 = 0%) and hypertensive populations (fixed effects, RR 0.97, 95% CI: 0.83–1.13, 513 deaths, χ^2 *P* value = 0.98, I^2 = 0%). Compared to control there was an increase in deaths with dietary salt reduction in the single heart failure study (fixed effects, RR: 2.59, 95% CI: 1.04–6.44, 21 deaths)[32] (see **Figure 2**).

In the three trials (TOHP I[33,34], TOHP II[34,45], and TONE[51]) with long-term follow-up which increased the total number of events available for analysis, there was still no strong evidence of a reduction in the number of deaths in the reduced salt group relative to controls, for the normotensives (fixed effects, RR 0.90, 95% CI: 0.58–1.40, 79 deaths, χ^2 *P* value = 1.00, I^2 = 0%) or hypertensive populations (fixed effects, RR 0.96, 95% CI: 0.83–1.11, 565 deaths, χ^2 *P* value = 0.92, I^2 = 0%) (see **Figure 3**).

CVD mortality was only reported in two studies of hypertensive patients. Both studies only reported trial end data. Chang *et al.* reported a lower proportion of CVD deaths in the reduced salt group (27 died; 1,310.0/100,000 person years) than in the control group (66 died; 2,140/100,000 person years).[19] Morgan *et al.* reported only five CVD deaths, three in the intervention, and two in control group.[30] The pooled RR was of consistent with more than a halving of the RR of CVD deaths or a small increase (fixed effects, RR 0.69, 95% CI: 0.45–1.05, 98 CVD deaths, χ^2 *P* value = 0.26, I^2 = 0%) (see **Figure 4**).

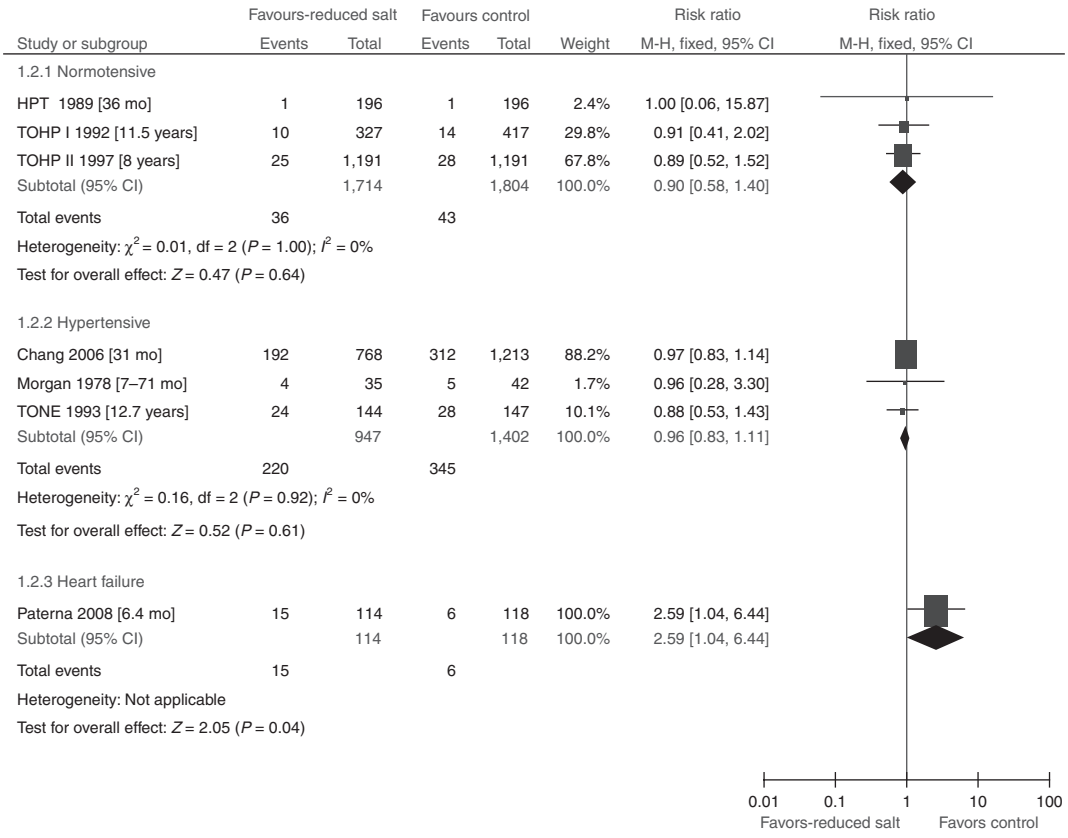

Figure 3 | All-cause mortality at longest follow-up. Duration of follow-up reported in parentheses.

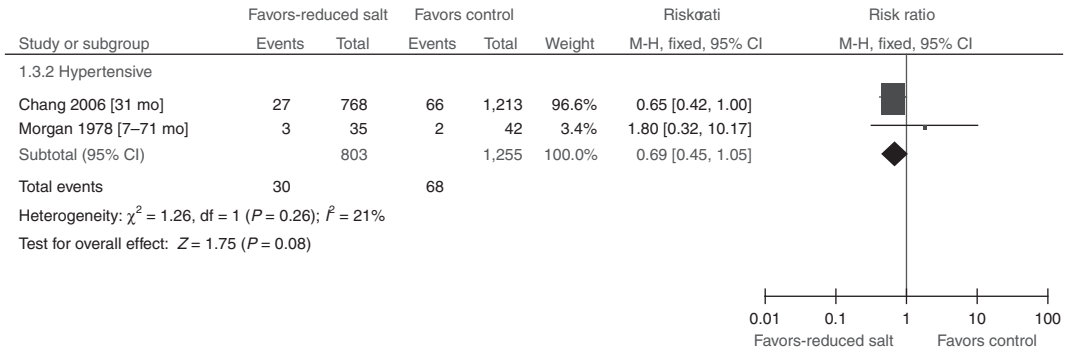

Figure 4 | Cardiovascular disease (CVD) mortality at longest follow-up. Duration of follow-up reported in parentheses.

Overall CVD morbidity was available for four trials (TOHP I[33,34], TOHP II, Morgan *et al.*[30], and TONE[51]). There was some evidence of statistical heterogeneity which may reflect that the definition of CVD morbidity varied between trials, although broadly consisted of composite of myocardial infarction, stroke, coronary artery bypass, angioplasty, or death from a CVD cause. At longer-term observational follow-up, TOHP I reported a RR reduction of CVD events of 49% (95% CI: 9–71%) with reduced salt although when pooled with long-term observational follow-up of TOHP II there was no strong evidence of benefit in normotensive participants (random effects, RR: 0.71, 95% CI: 0.42–1.20, 200 events, χ^2 *P* value = 0.10; I^2 = 63%).[34] There were no reports of CVD morbidity during or at the end of the randomized period for TOHP I or II studies. We found no strong evidence of benefits of salt reduction in hypertensive individuals (fixed effects, RR: 0.84, 95% CI: 0.57–1.24, 93 events, χ^2 *P* value = 0.53; I^2 = 0%) at end of trial (see **Figure 5**).

Individual CVD morbidity outcomes were infrequently reported and at trial end only. Paterna *et al.* reported 39 CVD-related hospital admissions (30 intervention, 9 control) in their study of congestive heart failure patients.[32] In TONE, at trial end, three patients experienced strokes (1 intervention, 2 control); 6 experienced a myocardial infarction (2 intervention, 4 control); 3 developed heart failure (2 intervention, 1 control), and 26 suffered from angina (9 intervention, 17 control).[51]

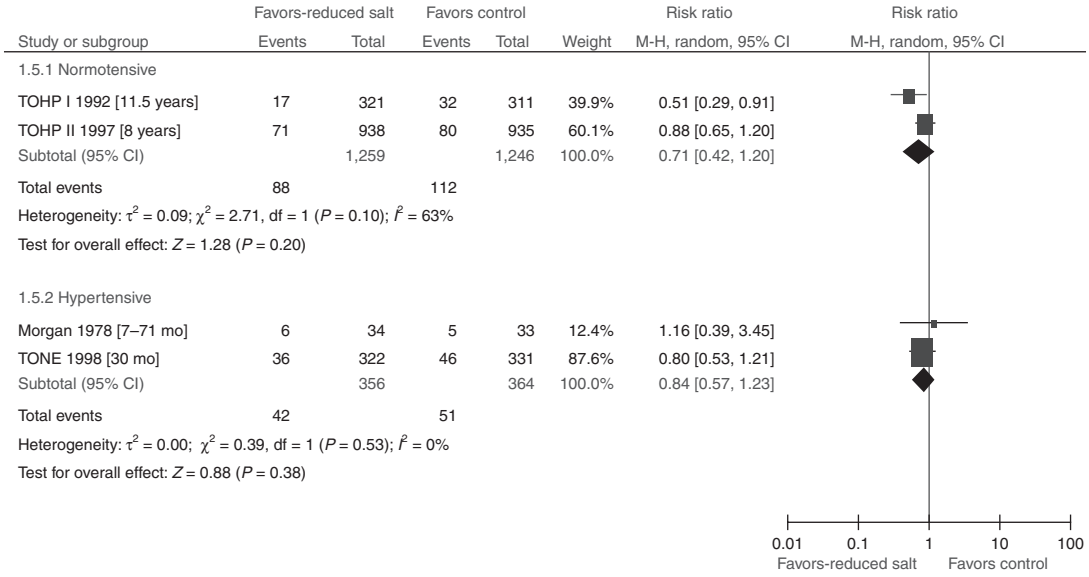

Figure 5 | Cardiovascular disease (CVD) events at longest follow-up. Duration of follow-up reported in parentheses.

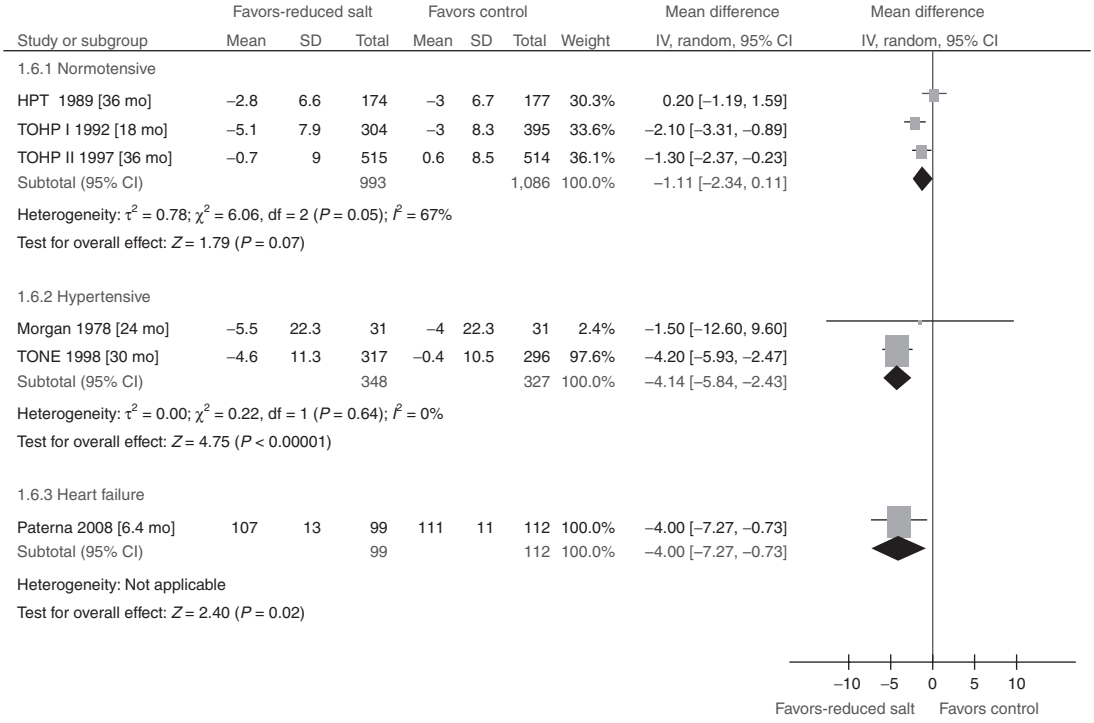

Figure 6 | Systolic blood pressure (BP) (mm Hg) at end of trial. Duration of follow-up reported in parentheses.

Blood pressure

End of trial BP was reported by all studies except Chang *et al.*[19] There was a evidence of substantial statistical heterogeneity. Systolic BP was reduced in all intervention arms of trials—normotensives (random effects, mean difference: 1.1 mm Hg, 95% CI: −0.1 to 2.3, χ^2 *P* value = 0.05, I^2 = 67%), hypertensives (fixed effect, mean difference 4.1 mm Hg, 95% CI: 2.4–5.8, χ^2 *P* value = 0.64; I^2 = 0%) and those with heart failure (by 4.0 mm Hg, 95% CI 0.7–7.3). Diastolic BP was also reduced in normotensives (fixed effect, mean difference: 0.8 mm Hg, 95% CI 0.2–1.4, χ^2 *P* value = 0.39); I^2 = 0%) but not in hypertensives (random effects, mean difference; 3.7 mm Hg, 95% CI: −0.9 to 8.4, χ^2 *P* value = 0.08; I^2 = 67%) or those with heart failure (mean difference: 2.0 mm Hg, 95% CI: −0.70 to 4.80) (see **Figures 6** and **7**).

Urinary sodium excretion

Changes in urinary sodium excretion at the end of trial were reported by all studies except Chang *et al.*[19] There was some

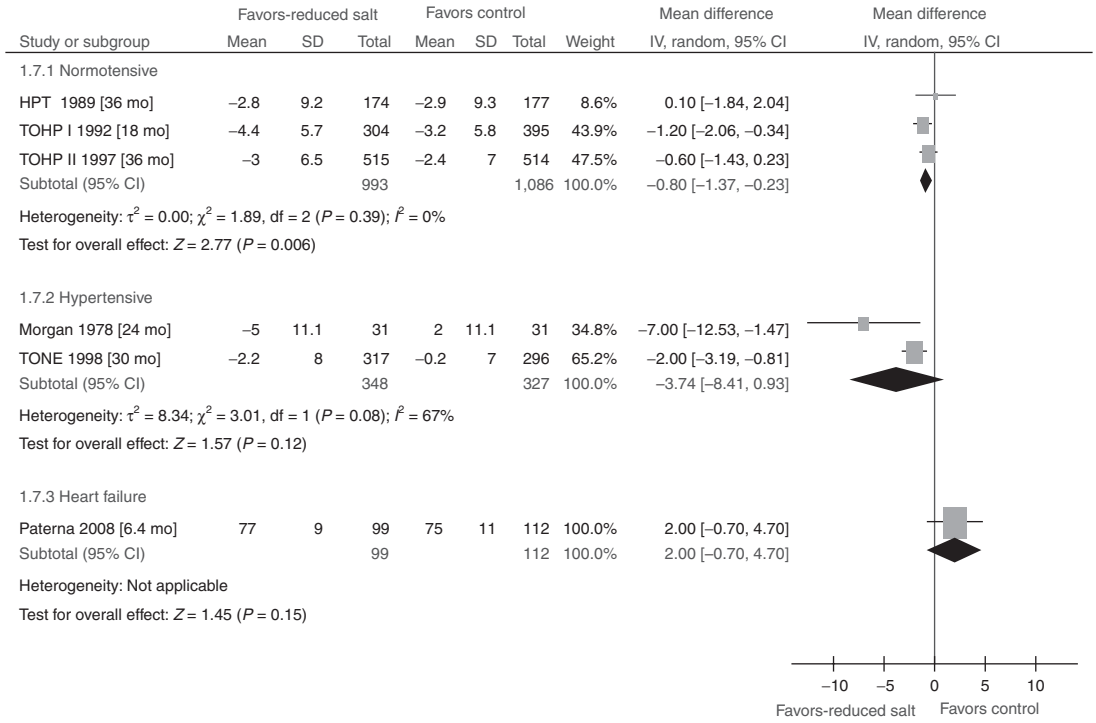

Figure 7 | Diastolic blood pressure (BP) (mm Hg) at end of trial. Duration of follow-up reported in parentheses.

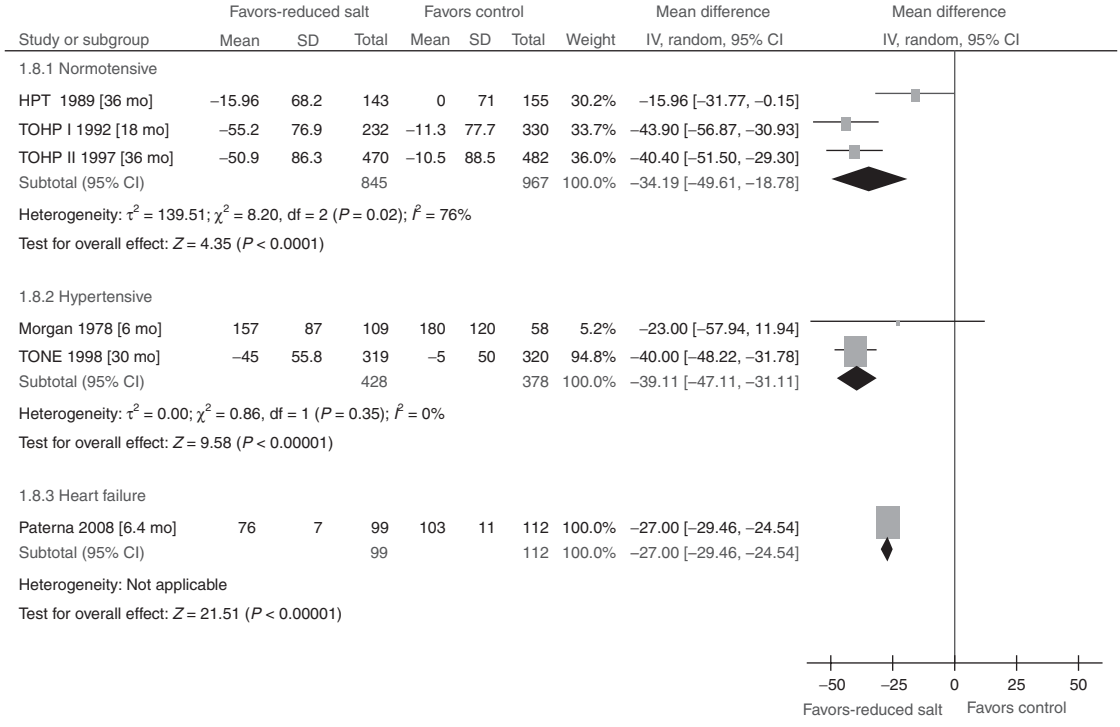

Figure 8 | Urinary sodium excretion (mmol/24 h) at end of trial. Duration of follow-up reported in parentheses.

evidence of statistical heterogeneity which may reflect different approaches to the assessment of 24-h urinary sodium excretion. In the study by Morgan *et al.*, results were only reported as samples and therefore contain repeated observations for a number of patients.[30] As for BP, in a number of studies, the last urinary sodium excretion available was at a time point much preceding the timing of the report mortality or CVD events (BP follow-up time: Morgan *et al.*[30]—6 months; TONE[51]—30 months, TOHP I[33]—18 months, TOHP II[45]—36 months). Urinary 24-h urinary sodium excretion was reduced by a similar amount across the three study subgroups—normotensives (random effects, mean difference: 34.2 mmol/24 h,

95% CI: 18.8–49.6, χ^2 P value = 0.03, I^2 = 76%), hypertensive (fixed effects, mean difference: 39.1 mmol/24 h, 95% CI: 31.1–47.1, χ^2 P value = 0.35; I^2 = 0%) and heart failure (mean difference: 27.0 mmol/24 h, 95% CI: 24.5–29.5) (see **Figure 8**).

Health-related quality of life

No studies reported outcomes using a validated health-related quality of life instrument.

DISCUSSION

This Cochrane review identified seven RCTs (in 6,257 individuals) of interventions aimed at reducing dietary salt on mortality and CVD morbidity with follow-up of 6 months or longer.[19,20,30,32,33,45,51] We found no strong evidence that salt reduction reduced all-cause mortality or CVD morbidity in normotensives or hypertensives. A single RCT showed an increase in the risk of all-cause death in those with congestive heart failure receiving a low-sodium diet.[32]

The interventions used were capable of reducing urinary sodium excretion and indicated that participants continued to comply with sodium restriction in the long-term, although, as noted in a previous Cochrane review, the degree of sodium restriction is likely to attenuate over time.[10] End of trial systolic and diastolic BPs were reduced by an average of some 1 mm Hg in normotensives and by an average of 2–4 mm Hg in hypertensives and those with heart failure. Sustained long-term reductions of BP of 1 and 4 mm Hg would be predicted to reduce CVD mortality by 5% and 20%, respectively.[58] Our point estimates are consistent with effects of this size but have wide CIs owing to the relatively small numbers of events.

Comparison to previous reviews

Our finding of a lack of strong evidence of an effect of dietary sodium reduction on mortality and CVD outcomes is in contrast to Strazzullo and colleagues who systematically reviewed prospective observational studies that examined the relationship between dietary sodium and all-cause mortality and CVD mortality.[6] They included 13 cohort studies over a follow-up 3–17 years and found higher salt intake to be associated with a greater risk of stroke (pooled RR: 1.23, 95% CI: 1.06–1.43, 5,346 stroke events) and CVD events (pooled RR: 1.14, 95% CI: 0.99–1.32, 5,161 CVD events). Total and CVD mortality were not reported. However, an inherent limitation of this review is the observational nature of the evidence which is open to confounding. These studies describe the outcomes for people who choose to follow a low-salt diet but provide no information about what might happen if that diet were experimentally allocated. People who choose a lower salt diet are likely to also eat a diet of fresh foods, lower in fats and refined carbohydrate, take more exercise and be less likely to smoke, so that their lower levels of deaths and disease may not relate to salt intake at all.

Strengths and limitations

We comprehensively searched for RCTs of dietary sodium reduction of 6 months or more that reported mortality or CVD events. We attempted to contact all authors of included studies to verify events. Because of longer observational follow-up (up to 10–15-years) of three of the trials included in the previous Cochrane review (TOHP I[33,34], TOHP II[34,45], and TONE[51]) and inclusion of two more recent RCTs (Chang *et al.*[19] and Paterna *et al.*[32]) we have been able to gather together more evidence on mortality and CVD outcomes (~6,250 participants, 665 deaths, 293 CVD events). Nevertheless the total amount of evidence on events remains relatively small. Assuming a control risk of 14% (Morgan *et al.*[30]) would require some 2,500 CVD events in order to detect a small reduction in RR (0.90) with dietary salt advice (at 80% power and 5% alpha). Our meta-analysis only had 10% power to detect a 10% reduction in RR.

Although all RCTs, only two of the seven included studies provided sufficient detail to be judged as having adequate random sequence generation, allocation concealment, and outcome blinding.[20,51] Nevertheless, all trials provided evidence of baseline balance. Although lack of blinding is unlikely to alter outcome assessment when outcomes include mortality and CVD events, failure to blind participant may have led to a positive change in the lifestyle and dietary behaviors behavior of control participants, reducing any difference between the groups.

Most trials appeared to be free from other dietary changes in the intervention and control group apart from dietary sodium. The one major exception was the trial by Chang *et al.* where sodium was replaced by a high potassium substitute.[19] Potassium has beneficial effects on BP but may have deleterious effects in individuals with renal disease.[59] Two studies in hypertensives allowed changes in antihypertensive medication during the period of the trial.[30,51] In both trials, lower levels of hypertensive medication in the intervention group compared to control may have reduced the BP-lowering effect of reduced dietary sodium and therefore offset mortality and CVD morbidity benefits.

In order to maximize the number of deaths and CVD events, we attempted to include data at the longest follow-up point. However, in doing so we may have introduced a major source of bias. For three large studies (TOHP I[33,34], TOHP II[34,45], and TONE[51]) the longest follow-up was considerably beyond the official end of the trial. It was therefore unclear if the intervention groups continued their low-salt diets and whether control groups were left to continue with dietary advice or advised to reduce their salt. Furthermore, reporting of long-term non-protocol defined analyses may be prone to selective reporting of outcomes showing benefits and nonpublication of negative findings. For this reason, we included the primary analysis in each case as the latest data at trial end, which was more robust but with slightly fewer deaths and CVD events.

Implications for practice

Our findings are consistent with the belief that salt reduction is beneficial in normotensive and hypertensive people. However, the methods of achieving salt reduction in the trials included in our review, and other systematic reviews, were relatively

modest in their impact on sodium excretion and on BP levels, generally required considerable efforts to implement and would not be expected to have major impacts on the burden of CVD. The challenge for clinical and public health practice is to find more effective interventions for reducing salt intake that are both practicable and inexpensive.

Many countries have national authoritative recommendations, often sanctioned by government, that call for reduced dietary sodium. For example, in UK, the National Institute of Health and Clinical Guidance (NICE) has recently called for an acceleration of the reduction in salt in the general population from a maximum intake of 6 g/day per adult by 2015 and 3 g by 2025.[1] Internationally, there are calls for a dietary salt reduction to be a major intervention for prevention and control noncommunicable diseases.[60] Voluntary reductions in hidden salt by the food industries and dietary advice to individuals are promoted as the best available interventions. Our review focuses on dietary advice and has not found robust evidence to support this approach.

Implications for research

In accord with the research recommendation of a previous Cochrane review, three of the large trials (TOHP I[33,34], TOHP II[34,45], and TONE[51]) have assessed the long-term effects of reduced dietary salt advice on mortality and CVD morbidity.[10] Our findings support the recent call for further rigorous large long-term RCTs, capable of definitively demonstrating the CVD benefit of dietary salt reduction.[5] Such trials need to incorporate population level interventions that are likely to lead to sustained reductions in salt intake commensurate with current guidelines. Further RCTs are needed to confirm if the dietary restriction of sodium is harmful for people with heart failure. It will be important to evaluate the effects of voluntary salt reductions by food industries as these may hold greater opportunities for practicable and inexpensive means of reducing salt intake in the population at large than focusing on dietary advice for individuals.[61]

Acknowledgments: We thank the authors of the included studies who provided additional information and the Cochrane Heart Group editorial team for comments on drafts of this review. This study was supported by a UK NIHR Cochrane Collaboration Programme grant "Cochrane Heart Public Health and Prevention Reviews" CPGS10.

Disclosure: The authors declared no conflict of interest.

1. National Institute for Health & Clinical Excellence (NICE). Prevention of cardiovascular disease at population level. 2010. Public Health Guidance 25. www.nice.org.uk/guidance/PH25 2010.
2. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J; National High Blood Pressure Education Program Coordinating Committee. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 2002; 288:1882–1888.
3. He FJ, MacGregor GA. Reducing population salt intake worldwide: from evidence to implementation. *Prog Cardiovasc Dis* 2010; 52:363–382.
4. He J, Whelton PK. Salt intake, hypertension and risk of cardiovascular disease: an important public health challenge. *Int J Epidemiol* 2002; 31:327–331; discussion 331.
5. Alderman MH. Reducing dietary sodium: the case for caution. *JAMA* 2010; 303:448–449.
6. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009; 339:b4567.
7. Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. *BMJ* 1996; 312:1249–1253.
8. He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev* 2004;CD004937.
9. Jürgens G, Graudal NA. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride. *Cochrane Database Syst Rev* 2004;CD004022.
10. Hooper L, Bartlett C, Davey SG, Ebrahim S. Advice to reduce dietary salt for prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2004;CD003656.
11. Elliott P. Sodium and blood pressure: a review of the evidence from controlled trials of sodium reduction and epidemiological studies. *Klin Wochenschr* 1991; 69 Suppl 25:3–10.
12. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.2. The Cochrane Collaboration, 2009.
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151:264–9, W64.
14. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993; 31:247–263.
15. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997; 315:1533–1537.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557–560.
17. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; 21:1559–1573.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629–634.
19. Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, Tsai SY, Pan WH. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *Am J Clin Nutr* 2006; 83:1289–1296.
20. Hypertension Prevention Trial Research Group. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. *Arch Intern Med* 1990; 150:153–162.
21. Borhani NO, Tonascia J, Schlundt DG, Prineas RJ, Jefferys JL. Recruitment in the Hypertension Prevention trial. Hypertension Prevention Trial Research Group. *Control Clin Trials* 1989; 10:30S–39S.
22. Brown KM, Oberman A, Van Natta ML, Forster JL. Baseline characteristics in the Hypertension Prevention Trial. Hypertension Prevention Trial Research Group. *Control Clin Trials* 1989; 10:40S–64S.
23. Forster JL, Jeffery RW, VanNatta M, Pirie P. Hypertension prevention trial: do 24-h food records capture usual eating behavior in a dietary change study? *Am J Clin Nutr* 1990; 51:253–257.
24. Jeffery RW, French SA, Schmid TL. Attributions for dietary failures: problems reported by participants in the Hypertension Prevention Trial. *Health Psychol* 1990; 9:315–329.
25. Jeffery RW, Tonascia S, Bjornson BW, Schlundt DG, Sugars C for the Hypertension Prevention Trial Research Group. Treatment in the hypertension prevention trial. *Controlled Clin Trials* 1989; 10(3 Suppl):65–83S.
26. Meinert CL, Borhani NO, Langford HG. Design, methods, and rationale in the Hypertension Prevention Trial. Hypertension Prevention Trial Research Group. *Control Clin Trials* 1989; 10:1S–29S.
27. Prud'homme GJ, Canner PL, Cutler JA. Quality assurance and monitoring in the Hypertension Prevention Trial. Hypertension Prevention Trial Research Group. *Control Clin Trials* 1989; 10:84S–94S.
28. Schmid TL, Jeffery RW, Onstad L, Corrigan SA. Demographic, knowledge, physiological, and behavioral variables as predictors of compliance with dietary treatment goals in hypertension. *Addict Behav* 1991; 16:151–160.
29. Shah M, Jeffery RW, Laing B, Savre SG, Van Natta M, Strickland D. Hypertension Prevention Trial (HPT): food pattern changes resulting from intervention on sodium, potassium, and energy intake. Hypertension Prevention Trial Research Group. *J Am Diet Assoc* 1990; 90:69–76.
30. Morgan T, Adam W, Gillies A, Wilson M, Morgan G, Carney S. Hypertension treated by salt restriction. *Lancet* 1978; 1:227–230.
31. Morgan TO, Adams WR, Hodgson M, Gibberd RW. Failure of therapy to improve prognosis in elderly males with hypertension. *Med J Aust* 1980; 2:27–31.
32. Paterna S, Gaspare P, Fasullo S, Sarullo FM, Di Pasquale P. Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend? *Clin Sci* 2008; 114:221–230.

33. The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels: results of the Trials of Hypertension Prevention, Phase I. *JAMA* 1992;267:1213–1220.
34. Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007; 334:885–888.
35. Cook NR, Kumanyika SK, Cutler JA. Effect of change in sodium excretion on change in blood pressure corrected for measurement error. The Trials of Hypertension Prevention, Phase I. *Am J Epidemiol* 1998; 148:431–444.
36. He J, Whelton PK, Appel LJ, Charleston J, Klag MJ. Long-term effects of weight loss and dietary sodium reduction on incidence of hypertension. *Hypertension* 2000; 35:544–549.
37. Kumanyika SK, Hebert PR, Cutler JA, Lasser VI, Sugars CP, Steffen-Batey L, Brewer AA, Cameron M, Shepek LD, Cook NR. Feasibility and efficacy of sodium reduction in the Trials of Hypertension Prevention, phase I. Trials of Hypertension Prevention Collaborative Research Group. *Hypertension* 1993; 22:502–512.
38. Sacks FM, Hebert P, Appel LJ, Borhani NO, Applegate WB, Cohen JD, Cutler JA, Kirchner KA, Kuller LH, Roth KJ. Short report: the effect of fish oil on blood pressure and high-density lipoprotein-cholesterol levels in phase I of the Trials of Hypertension Prevention. *J Hypertens* 1994; 12:209–213.
39. Satterfield S, Cutler JA, Langford HG, Applegate WB, Borhani NO, Brittain E, Cohen JD, Kuller LH, Lasser NL, Oberman A. Trials of hypertension prevention. Phase I design. *Ann Epidemiol* 1991; 1:455–471.
40. Stevens VJ, Corrigan SA, Obarzanek E, Bernauer E, Cook NR, Hebert P, Mattfeldt-Beman M, Oberman A, Sugars C, Dalcin AT. Weight loss intervention in phase 1 of the Trials of Hypertension Prevention. The TOHP Collaborative Research Group. *Arch Intern Med* 1993; 153:849–858.
41. Whelton PK, Buring J, Borhani NO, Cohen JD, Cook N, Cutler JA, Kiley JE, Kuller LH, Satterfield S, Sacks FM. The effect of potassium supplementation in persons with a high-normal blood pressure. Results from phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995; 5:85–95.
42. Whelton PK, Kumanyika SK, Cook NR, Cutler JA, Borhani NO, Hennekens CH, Kuller LH, Langford H, Jones DW, Satterfield S, Lasser NL, Cohen JD. Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group. *Am J Clin Nutr* 1997; 65:652S–660S.
43. Whelton PK, Hebert PR, Cutler J, Applegate WB, Eberlein KA, Klag MJ, Keough ME, Hamill S, Borhani NO, Hollis J. Baseline characteristics of participants in phase I of the Trials of Hypertension Prevention. *Ann Epidemiol* 1992; 2:295–310.
44. Yamamoto ME, Applegate WB, Klag MJ, Borhani NO, Cohen JD, Kirchner KA, Lakatos E, Sacks FM, Taylor JO, Hennekens CH. Lack of blood pressure effect with calcium and magnesium supplementation in adults with high-normal blood pressure. Results from Phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995; 5:96–107.
45. The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. *Arch Intern Med* 1997; 157:657–667.
46. Appel LJ, Hebert PR, Cohen JD, Obarzanek E, Yamamoto M, Buring J, Stevens V, Kirchner K, Borhani NO. Baseline characteristics of participants in phase II of the Trials of Hypertension Prevention (TOHP II). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995; 5:149–155.
47. Hebert PR, Bolt RJ, Borhani NO, Cook NR, Cohen JD, Cutler JA, Hollis JF, Kuller LH, Lasser NL, Oberman A. Design of a multicenter trial to evaluate long-term life-style intervention in adults with high-normal blood pressure levels. Trials of Hypertension Prevention (phase II). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995; 5:130–139.
48. Hollis JF, Satterfield S, Smith F, Fouad M, Allender PS, Borhani N, Charleston J, Hirlinger M, King N, Schultz R. Recruitment for phase II of the Trials of Hypertension Prevention. Effective strategies and predictors of randomization. Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995; 5:140–148.
49. Hunt SC, Cook NR, Oberman A, Cutler JA, Hennekens CH, Allender PS, Walker WG, Whelton PK, Williams RR. Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension: trials of hypertension prevention, phase II. *Hypertension* 1998; 32:393–401.
50. Lasser VI, Raczynski JM, Stevens VJ, Mattfeldt-Beman MK, Kumanyika S, Evans M, Danielson E, Dalcin A, Batey DM, Belden LK. Trials of Hypertension Prevention, phase II. Structure and content of the weight loss and dietary sodium reduction interventions. Trials of Hypertension Prevention (TOHP) Collaborative Research Group. *Ann Epidemiol* 1995; 5:156–164.
51. Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH Jr, Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA* 1998; 279:839–846.
52. Appel LJ, Espeland M, Whelton PK, Dolecek T, Kumanyika S, Applegate WB, Ettinger WH Jr, Kostis JB, Wilson AC, Lacy C. Trial of Nonpharmacologic Intervention in the Elderly (TONE). Design and rationale of a blood pressure control trial. *Ann Epidemiol* 1995; 5:119–129.
53. Appel LJ, Espeland MA, Easter L, Wilson AC, Folmar S, Lacy CR. Effects of reduced sodium intake on hypertension control in older individuals: results from the Trial of Nonpharmacologic Interventions in the Elderly (TONE). *Arch Intern Med* 2001; 161:685–693.
54. Bahnson JL, Whelton PK, Appel LJ, Espeland MA, Wofford JL, Rosen R, Wilson AC, Lacey CR, Rutan G, Hogan P, Tayback M, Dolecek TA, Shindler D. Baseline characteristics of randomized participants in the trial of nonpharmacologic intervention in the elderly (TONE). *Disease Management and Clinical Outcomes* 1997; 1:61–68.
55. Espeland MA, Whelton PK, Kostis JB, Bahnson JL, Ettinger WH, Cutler JA, Appel LJ, Kumanyika S, Farmer D, Elam J, Wilson AC, Applegate WB. Predictors and mediators of successful long-term withdrawal from antihypertensive medications. TONE Cooperative Research Group. Trial of Nonpharmacologic Interventions in the Elderly. *Arch Fam Med* 1999; 8:228–236.
56. Kostis JB, Espeland MA, Appel L, Johnson KC, Pierce J, Wofford JL. Does withdrawal of antihypertensive medication increase the risk of cardiovascular events? Trial of Nonpharmacologic Interventions in the Elderly (TONE) Cooperative Research Group. *Am J Cardiol* 1998; 82:1501–1508.
57. Whelton PK, Babnson J, Appel LJ, Charleston J, Cosgrove N, Espeland MA, Folmar S, Hoagland D, Krieger S, Lacy C, Lichtermann L, Oates-Williams F, Tayback M, Wilson AC. Recruitment in the Trial of Nonpharmacologic Intervention in the Elderly (TONE). *J Am Geriatr Soc* 1997; 45:185–193.
58. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335:765–774.
59. Cappuccio FP. Sodium, potassium, calcium and magnesium and cardiovascular risk. *J Cardiovasc Risk* 2000; 7:1–3.
60. Beaglehole R, Bonita R, Horton R, Adams C, Alleyne G, Asaria P, Baugh V, Bekedam H, Billo N, Casswell S, Cecchini M, Colagiuri R, Colagiuri S, Collins T, Ebrahim S, Engelgau M, Galea G, Gaziano T, Geneau R, Haines A, Hospedales J, Jha P, Keeling A, Leeder S, Lincoln P, McKee M, Mackay J, Magnusson R, Moodie R, Mwatsama M, Nishtar S, Norrving B, Patterson D, Piot P, Ralston J, Rani M, Reddy KS, Sassi F, Sheron N, Stuckler D, Suh I, Torode J, Varghese C, Watt J; Lancet NCD Action Group; NCD Alliance. Priority actions for the non-communicable disease crisis. *Lancet* 2011; 377:1438–1447.
61. Cobiac LJ, Vos T, Veerman JL. Cost-effectiveness of interventions to reduce dietary salt intake. *Heart* 2010; 96:1920–1925.